

Original article

Validation of the self-administered comorbidity questionnaire adjusted for spondyloarthritis: results from the ASAS-COMOSPA study

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Abstract

Objective. To confirm validity of the Self-administered Comorbidity Questionnaire modified for patients with SpA (mSCQ), and assess whether validity improves when adding items on extra-articular manifestations (EAMs), i.e. uveitis, psoriasis, and IBD, and osteoporosis and fractures.

Methods. Data from the Assessment in SpondyloArthritis international Society COMORbidities in SPondyloArthritis study were used. Criterion validity of presence of EAMs, osteoporosis and fractures was assessed as agreement (kappa) between patients' self-reported and physician-confirmed disease. Construct validity of the mSCQ including EAMs, osteoporosis and/or fractures (SpA-SCQ) was assessed by testing hypotheses about correlations with demographics, physical function, work ability, health utility and disease activity, and was compared with construct validity of the rheumatic disease comorbidity index.

Results. In total, 3984 patients contributed to the analyses. Agreement between patient-reported and physician-reported EAMs was substantial to almost perfect (uveitis $\kappa = 0.81$, IBD $\kappa = 0.73$, psoriasis $\kappa = 0.86$). Agreement for osteoporosis ($\kappa = 0.38$) and fractures ($\kappa = 0.39$) was fair. As hypothesized, the mSCQ correlated moderately to weakly with age, physical function, work limitations and health utility, and very weakly with disease activity. In contrast to our hypothesis, adding EAMs, osteoporosis and/or fractures to the mSCQ decreased correlations with several external constructs, especially among patients with peripheral SpA. Correlations with the different constructs were stronger for the both mSCQ and SpA-SCQ ($r_{\text{BASFI}} = 0.34$; $r_{\text{EQ-5D}} = -0.33$) compared with the rheumatic disease comorbidity index ($r_{\text{BASFI}} = 0.24$; $r_{\text{EQ-5D}} = -0.21$).

Conclusion. The mSCQ is a valid self-report instrument to assess the influence of comorbidities on health outcomes in patients with SpA. Adding EAMs and/or osteoporosis or fractures does not improve validity of the mSCQ.

Key words: spondyloarthritis, axial spondyloarthritis, peripheral spondyloarthritis, comorbidity, extra-articular manifestations, comorbidity questionnaire, validity

Rheumatology key messages

- The mSCQ is a valid instrument to assess comorbidity in patients with SpA.
- Patients with SpA can accurately report extra-articular manifestations.
- Adding EAMs or fractures to the SpA-mSCQ does not improve validity of the questionnaire.

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Introduction

In addition to axial and peripheral joint disease, patients with spondyloarthritis (SpA) can have one or more extra-articular manifestations (EAMs), including acute anterior uveitis (AAU), psoriasis and IBD [1]. These EAMs are recognized to be part of the SpA disease concept, and contribute to the diagnosis of SpA [2], as reflected in the current classification criteria [3, 4]. Patients with SpA may also develop diseases that are not related to the SpA concept, but that may co-exist with the main disease, as a consequence of the disease process or its treatment, and which are called comorbidities. Both, EAMs and comorbidities have been associated with impaired physical and mental functioning, restricted participation in social roles and increased health care costs [5–7]. It has been shown that EAMs and comorbidities influence the choice of drug treatment [8] and contribute to the complexity of management of patients [9].

To assess the influence of comorbidities on functioning and health in patients with ankylosing spondylitis (AS), the self-administered comorbidity questionnaire (SCQ) was validated in 98 patients with AS in the Outcome in AS International Study (OASIS) [10, 11]. This study showed evidence for criterion and construct validity of the SCQ in patients with long-standing AS, who fulfilled the New York criteria for AS and were under care of a rheumatologist in three tertiary centres in Europe. The validity improved after removing rheumatic items (chronic rheumatic disease, back pain and osteoarthritis) from the original questionnaire, which led to the development of a modified SCQ (mSCQ) for AS [10]. However, it is not known whether the mSCQ has also validity in a broader, more heterogeneous group of patients with axial (with and without radiographic involvement) as well as peripheral SpA. Moreover, as EAMs frequently occur in this population and can impact health outcomes, it can be expected that adding EAMs to the mSCQ may improve the validity of the questionnaire. Furthermore, the mSCQ includes common comorbidities, such as cardiovascular disease, but not yet comorbidities that are more frequent in SpA compared with the general population, such as fractures and osteoporosis, and which might impact functioning and health in SpA.

Therefore, the aims of the current study were to confirm the construct validity of the mSCQ in a heterogeneous group of patients with SpA, to evaluate whether EAMs, osteoporosis and fractures can be reliably assessed using self-report, and to assess whether ‘adding’ EAMs, osteoporosis and/or fractures improves the construct validity of the mSCQ with regard to (aspects of) functioning and health.

Methods

Patients

This study was conducted using the Assessment in SpondyloArthritis international Society (ASAS) COMOrbidities in Spondyloarthritis (ASAS-COMOSPA)

dataset, which has been described elsewhere [12]. In summary, ASAS-COMOSPA is an observational, cross-sectional, multicentre, international study. In total, 22 countries participated and included consecutive patients of at least 18 years with a clinical diagnosis of axial SpA (axSpA) or peripheral SpA (pSpA) according to the rheumatologist. Patients had to be able to understand and complete the questionnaire. The study was conducted according to guidelines for good clinical practice in each country, with all local ethics committees approving the ASAS-COMOSPA study protocol. All patients signed informed consent before enrolment [12].

Assessments

Demographics and disease characteristics

For each patient, demographics and disease characteristics, such as axial or peripheral involvement, arthritis and enthesitis, were collected. Disease activity was measured by the ASDAS including CRP [13], physical function by the BASFI [14], well-being by the patient global assessment score [15], and health utility by the EuroQoL 5 dimensions questionnaire (EQ-5D) [16]. Restrictions in paid or unpaid work in the past 7 days due to health problems were assessed using the Work Productivity and Activity Impairment questionnaire [17].

Comorbidities and EAMs

The presence or history of commonly occurring and important comorbidities in SpA was collected by the study investigator or research nurse during a face-to-face interview at the study visit, ascertained by a review of the medical record and current medication use. Comorbidities included ischaemic cardiovascular disease (myocardial infarction and stroke), cancer (lung, colon, skin, breast and cervix for women, prostate for men, and lymphoma), osteoporosis (defined as (i) a T-score < -2.5 S.D. at either the total hip or lumbar spine or the femoral neck, (ii) a history of a vertebral or peripheral non-traumatic fracture, (iii) a past history or current treatment with a specific anti-osteoporotic drug, or (iv) a history of diagnosis of secondary osteoporosis), gastrointestinal disease (a history of gastroduodenal ulcer and diverticulitis), hypertension and diabetes. The presence or history of EAMs [AAU, IBD (Crohn’s disease or ulcerative colitis) and psoriasis, diagnosed by an ophthalmologist for AAU or physician for IBD and psoriasis] was obtained by the study investigator by review of the medical record and by interviewing the patient.

The mSCQ

The mSCQ is a self-reported questionnaire [10]. The mSCQ asks whether the patient suffers currently from one or more of 10 medical conditions (heart disease, hypertension, lung disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anaemia or other blood disease, cancer, and depression), and an option to add three other not pre-specified medical problems [11]. The patient is asked to indicate for each condition if it is present (yes/no), is currently treated (yes/no), and/or

imposes functional limitations (yes/no). Every 'yes' is given 1 point contributing to a maximum score of 39. For the present study, different SpA-specific versions of the mSCQ (SpA-SCQ) were computed by adding uveitis, psoriasis, IBD, with or without osteoporosis and/or fractures. The SpA-SCQ versions are scored similarly to the mSCQ but due to additional items, the score for the most extensive version ranges from 0 to 54. The mSCQ and questions on EAMs were translated by the national principal investigators in the appropriate language, in which they were instructed to use layman's terms (e.g. add short descriptions to the name of the condition) in order to make the mSCQ as clear as possible for patients.

The RDCI

The Rheumatic Disease Comorbidity Index (RDCI) is a validated instrument to reflect the burden of comorbidity on functioning and mortality [18]. The RDCI (score 0–9) is calculated using the following formula: $2 \times \text{lung disease} + [2 \times (\text{heart attack, other CV, or stroke}) \text{ or } 1 \times \text{hypertension}] + \text{fracture} + \text{depression} + \text{diabetes} + \text{cancer} + (\text{ulcer or stomach problem})$. In the present study, information on physician-reported comorbidities were used to calculate the RDCI, except for depression that was based on patients' self-reporting, because this item was not included in the CRF of the study investigator in COMOSPA.

Statistics

Descriptive statistics were used to characterize the study sample, using mean with standard deviation for continuous data, and frequencies were calculated for dichotomous data.

Criterion validity

Agreement between self-reported EAMs, osteoporosis and fractures with comorbidities reported by the study investigator was evaluated using Cohen's kappa. A kappa value of <0.001 was considered as poor agreement, 0.001–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1.00 as almost perfect agreement [19].

Construct validity

For construct validity, the correlation between comorbidity scores and continuous external constructs was evaluated using Spearman's correlation coefficient. Correlation coefficients of 0.01–0.20 were considered as very weak, 0.21–0.40 as weak, 0.41–0.75 as moderate and above 0.75 as strong [20]. First, the correlations between the different versions of the mSCQ and the RDCI were calculated and (very) strong correlations would indicate that both approaches to assess comorbidities would actually be interchangeable. Second, the predetermined hypothesis was tested that the mSCQ correlates *moderately* with age, physical function (measured with the BASFI), health utility (measured with the EQ-5D using the French tariff for all patients), patient's global assessment of well-being assessment of well-being, productivity at work and impact on regular activities, but *very weak* with disease activity (measured with the ASDAS-CRP). Next, the correlations

with the constructs of the different versions of the SpA-SCQ (mSCQ + EAMs, mSCQ + osteoporosis + fractures, and mSCQ + EAMs + osteoporosis and/or fractures) and the RDCI were compared with the mSCQ. The predetermined hypothesis was that SpA-SCQ versions would correlate better with physical function, quality of life, work ability and patient's global score of well-being. A change of 10% of the correlation coefficient was considered as a relevant improvement.

Analyses were repeated for the subgroups of patients fulfilling either the ASAS axSpA or pSpA criteria. Furthermore, an additional explorative analysis was performed to understand whether there are differences in validity between different regions of the world. For all outcomes, differences in correlation coefficients of 10% between groups were considered as relevant. All analyses were performed using SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA).

Results

In total 4028 patients from 22 countries were included in ASAS-COMOSPA. Forty-four patients were excluded because all data except identification numbers were missing. Therefore, 3984 patients contributed to the current analysis [12]. Table 1 presents the clinical and demographic characteristics for the total group, and for axSpA and pSpA separately. The mean (s.d.) age was 43.6 (14.0) years, 2563 were male patients (65.0%), and the mean (s.d.) disease duration was 8.2 (9.3) years. In total, 2955 (75%) patients fulfilled the ASAS criteria for axSpA and 415 (10.4%) patients fulfilled the ASAS criteria for pSpA; 614 (14.6%) patients did not fulfil any of the ASAS criteria [21]. The mean mSCQ score was 1.9 (s.d. 2.7, range 0–22). The mean score of the mSCQ including the three EAMs was 2.7 (s.d. 3.2, range 0–29), and the mean score of the mSCQ including EAMs, osteoporosis and fractures was 2.9 (s.d. 3.4, range 0–35). The mean RDCI score was 0.6 (s.d. 1.0, range 0–8). Patients who fulfilled the ASAS pSpA criteria were on average older and reported higher comorbidity scores on both the mSCQ and the RDCI compared with patients who fulfilled the ASAS axSpA criteria.

Supplementary Table S1, available at *Rheumatology* online, shows the baseline characteristics and mSCQ scores per region in the world. Patients from Europe and North America were on average older compared with those from other regions, and reported higher comorbidity scores.

The most frequently self-reported comorbidities were hypertension (820 patients, 20.6%), and depression (534 patients, 13.4%) (Table 2). Examples of frequently reported 'other medical conditions' were fibromyalgia (63 patients, 1.6%), thyroid disease (46 patients, 1.2%) and hypercholesterolaemia (38 patients, 1.0%). Hypertension was the comorbidity for which use of medication was reported most often (18.6%), and depression most frequently limited functioning (4.4%). Psoriasis was the most frequently reported EAM (22.1%), followed by uveitis (18.8%) and IBD (7.2%). Limitations in functioning caused

TABLE 1 Characteristics of the study sample

Characteristic	All patients (n = 3984)	ASAS Axial SpA (n = 2955)	ASAS Peripheral SpA (n = 415)
Male gender, n (%)	2563 (65.0)	1996 (67.5)	225 (54.2)
Age, mean (s.d.), years	43.6 (14.0)	41.7 (13.2)	51.1 (14.0)
Disease duration, mean (s.d.), years	8.2 (9.3)	8.6 (9.7)	6.4 (7.6)
HLA-B27 positive/negative/missing, n (%)	2217/844/923 (55.6/21.2/23.2)	1980/546/428 (67.0/18.5/14.5)	102/105/207 (24.6/25.3/49.9)
Current smoker, n (%)	914 (22.9)	717 (24.3)	66 (15.9)
BMI (kg/m ²), mean (s.d.)	26.1 (5.7)	25.9 (5.6)	27.6 (6.4)
Currently employed, n (%)	2325 (58.4)	1766 (59.8)	228 (54.9)
ASDAS-CRP, mean (s.d.)	2.0 (1.1)	2.0 (1.1)	2.0 (1.0)
BASFI (0–10), mean (s.d.)	3.0 (2.7)	3.1 (2.7)	2.8 (2.6)
EQ-5D (0–1), mean (s.d.)	0.59 (0.34)	0.58 (0.34)	0.57 (0.34)
Global well-being (0–10), mean (s.d.)	4.1 (2.6)	4.1 (2.5)	4.1 (2.6)
WPAI, impact on work productivity (0–10), mean (s.d.) ^{a,b}	2.8 (2.6)	2.8 (2.6)	2.9 (3.0)
Impact on daily activities (0–10), mean (s.d.) ^a	3.8 (2.9)	3.8 (2.9)	3.9 (2.9)
History of uveitis, n (%)	769 (19.3)	653 (22.1)	44 (10.6)
History of psoriasis, n (%)	841 (21.1)	371 (12.6)	240 (57.8)
History of IBD, n (%)	208 (5.2)	157 (5.3)	17 (4.1)
mSCQ (0–39), mean (s.d.); median (range)	1.9 (2.7); 1 (0–22)	1.8 (2.6); 0 (0–21)	2.5 (3.2); 2 (0–20)
mSCQ + EAMs (0–48), mean (s.d.); median (range)	2.7 (3.2); 2 (0–29)	2.4 (3.0); 1 (0–24)	3.8 (3.8); 3 (0–29)
mSCQ + osteoporosis + fractures (0–45), mean (s.d.); median (range)	2.1 (3.0); 1 (0–26)	2.0 (2.8); 1 (0–24)	2.7 (3.6); 2 (0–26)
mSCQ + EAMS + osteoporosis + fractures (0–54), mean (s.d.); median (range)	2.9 (3.4); 2 (0–35)	2.6 (3.2); 2 (0–27)	4.1 (4.2); 3 (0–35)
RDCI (0–9), mean (s.d.); median (range)	0.6 (1.0); 0 (0–8)	0.5 (1.0); 0 (0–8)	0.9 (1.2); 0 (0–8)

^aMeasured with the WPAI. ^bOnly in patients currently employed (n = 2325). ASAS: Assessment SpondyloArthritis international Society; EAM: extra-articular manifestation; EQ-5D: Euroqol 5 D; mSCQ: modified self-administered comorbidity questionnaire; SpA: spondyloarthritis; RDCI: rheumatic disease comorbidity instrument; WPAI: work productivity and activity impairment.

TABLE 2 Patients' responses on SpA-SCQ (n = 3984)

Response	Present, n (%)	Treatment, n (%)	Limitations, n (%)
Heart disease	220 (5.5)	177 (4.4)	85 (2.1)
Hypertension	820 (20.6)	743 (18.6)	100 (2.5)
Lung disease	159 (4.0)	120 (3.0)	65 (1.6)
Diabetes	201 (5.0)	181 (4.5)	59 (1.5)
Ulcer or stomach disease	421 (10.6)	346 (8.7)	82 (2.1)
Kidney disease	120 (3.0)	65 (1.6)	17 (0.4)
Liver disease	129 (3.2)	68 (1.7)	10 (0.3)
Anaemia/other blood disease	283 (7.1)	134 (3.4)	61 (1.5)
Cancer	60 (1.5)	39 (1.0)	15 (0.4)
Depression	534 (13.4)	268 (6.7)	177 (4.4)
Other medical problem 1 ^a	590 (14.8)	448 (11.2)	278 (7.0)
Other medical problem 2 ^a	170 (4.3)	112 (2.8)	57 (1.4)
Other medical problem 3 ^a	60 (1.5)	44 (1.1)	32 (0.8)
Uveitis	747 (18.8)	110 (2.8)	174 (4.4)
Psoriasis	880 (22.1)	483 (12.1)	175 (4.4)
Inflammatory bowel disease	288 (7.2)	115 (2.9)	73 (1.8)
Osteoporosis	295 (7.4)	203 (5.1)	74 (1.9)
Fractures	195 (4.9)	88 (2.2)	60 (1.5)

^aThe SCQ includes the option to fill in one to three other non-specified medical problems. SpA-SCQ: spondyloarthritis self-administered comorbidity questionnaire.

TABLE 3 Agreement between mSCQ and physician-reported EAMs and comorbidities

	Self-reported, <i>n</i> (%)	Physician reported, <i>n</i> (%)	Kappa
All patients (<i>n</i> = 3984)			
Uveitis	747 (18.8)	769 (19.3)	0.81
Psoriasis	880 (22.1)	841 (21.1)	0.86
Inflammatory bowel disease	288 (7.2)	208 (5.2)	0.73
Osteoporosis	295 (7.4)	529 (13.4)	0.38
Fractures	195 (4.9)	192 (4.8)	0.39
Axial SpA (<i>n</i> = 2955)			
Uveitis	635 (21.4)	646 (21.9)	0.82
Psoriasis	394 (13.3)	369 (12.5)	0.84
Inflammatory bowel disease	225 (7.6)	155 (5.2)	0.74
Osteoporosis	202 (6.8)	387 (13.1)	0.38
Fractures	138 (4.7)	145 (4.9)	0.37
Peripheral SpA (<i>n</i> = 415)			
Uveitis	43 (10.4)	44 (10.6)	0.76
Psoriasis	242 (58.3)	238 (57.3)	0.84
Inflammatory bowel disease	25 (6.0)	17 (4.1)	0.60
Osteoporosis	31 (7.4)	50 (12.0)	0.39
Fractures	18 (4.3)	12 (2.9)	0.38

by EAMs were reported by 4.4% of patients with uveitis and psoriasis, and by 1.8% of patients with IBD.

Criterion validity

Table 3 shows the frequency of self-reported EAMs, osteoporosis and fractures compared with the frequency of these conditions according to the study investigator, and agreement (kappa) between both. The agreement was almost perfect for uveitis ($\kappa=0.81$) and psoriasis ($\kappa=0.86$), substantial for inflammatory bowel disease ($\kappa=0.73$), and fair for osteoporosis and fractures ($\kappa=0.38$ and $\kappa=0.39$, respectively). Agreement was comparable for axial and peripheral SpA. Supplementary Table S2, available at *Rheumatology* online, shows the criterion validity per region in the world. For uveitis and IBD, the lowest kappa values were found in North Africa.

Construct validity

The correlation between the mSCQ and the SpA-SCQ (including EAMS and osteoporosis and/or fractures) was 0.79, between the mSCQ and RDCI 0.57, and between the SpA-SCQ and RDCI 0.54.

Table 4 shows the correlations of the mSCQ, the different SpA-SCQ versions and RDCI with different external constructs in the total group, and in the subgroups of patients with axSpA and pSpA. Supplementary Table S3, available at *Rheumatology* online, shows the construct validity by region in the world.

As hypothesized, the mSCQ correlated weakly to moderately with age and physical functioning, quality of life and patient's global. Correlation between the mSCQ and disease activity was very weak.

When adding EAMs to the mSCQ, correlation with age became better. However, in contrast to our hypothesis, correlations with patient's global assessment of well-

being, productivity at work and influence on daily activities became weaker. Correlations with BASFI and EQ-5D did not change. When adding osteoporosis or fractures to the mSCQ, no change in correlations was observed.

In subanalyses of patients with axSpA and pSpA, a stronger correlation of the mSCQ with BASFI was found in patients with pSpA, whereas in patients with axSpA a stronger correlation with EQ-5D was found. When EAMs were added to the mSCQ, correlations with most variables became weaker in patients with pSpA, whereas only correlation with productivity at work and disease activity became weaker in axSpA.

The RDCI, finally, showed weaker correlations with the different external constructs than the mSCQ and SpA-SCQ, except the correlation with age, which was stronger for the RDCI. For the RDCI, most correlations were stronger in pSpA patients compared with axSpA patients.

Construct validity of the different versions of the mSCQ with BASFI, EQ-5D and ASDAS-CRP were lower in Asia and North Africa, compared with other parts of the world.

Discussion

The present study confirms that the mSCQ is a valid instrument to assess the impact of comorbidities on physical functioning and quality of life in a real life multinational group of patients diagnosed with axSpA or pSpA. The mSCQ showed stronger correlations with different health outcomes, except for age, compared with the RDCI. Furthermore, we showed that patients can accurately report EAMs, but agreement between self-reported and physician-reported osteoporosis and fractures was weak. Finally, adding EAMs and/or osteoporosis and fractures to the mSCQ (SpA-SCQ) did not improve correlations with different health outcomes.

TABLE 4 Construct validity of different modifications of the mSCQ and the RDCI with health outcomes in all patients, and subgroups of patients with axSpA and pSpA

	Age	BASFI	EQ-5D	patient's global assessment of well-being	WPAI, impact on work productivity ^a	Impact on daily activities	ASDAS-CRP
All patients (n = 3984)							
mSCQ	0.41	0.34	-0.33	0.22	0.21	0.30	0.19
mSCQ + EAMs	0.45	0.32	-0.33	0.19 ^c	0.16 ^c	0.26 ^c	0.16 ^c
mSCQ + fractures	0.40	0.34	-0.33	0.21	0.20	0.29	0.19
mSCQ + osteoporosis + fracture	0.41	0.34	-0.33	0.22	0.21	0.30	0.19
mSCQ + EAMs + osteoporosis	0.46 ^c	0.32	-0.33	0.20	0.17 ^c	0.27	0.16 ^c
mSCQ + EAMs + fractures	0.45	0.32	-0.33	0.19 ^c	0.17 ^c	0.27	0.16 ^c
mSCQ + EAMs + osteoporosis + fractures	0.45	0.33	-0.33	0.20	0.17 ^c	0.27	0.17
RDCI ^b	0.47 ^c	0.24 ^c	-0.21 ^c	0.12 ^c	0.09 ^c	0.17 ^c	0.10 ^c
Patients fulfilling ASAS axSpA criteria (n = 2955)							
mSCQ	0.38	0.35 ^d	-0.35 ^d	0.21 ^d	0.20 ^d	0.29 ^d	0.19 ^d
mSCQ + EAMs	0.42 ^c	0.34	-0.34 ^d	0.20 ^d	0.17 ^{c,d}	0.27	0.17 ^{c,d}
mSCQ + fractures	0.38	0.35 ^d	-0.34 ^d	0.21 ^d	0.20 ^d	0.30 ^d	0.18 ^d
mSCQ + osteoporosis + fracture	0.39	0.35 ^d	-0.34	0.22 ^d	0.20 ^d	0.30 ^d	0.19 ^d
mSCQ + EAMs + osteoporosis	0.42 ^c	0.34	-0.34 ^d	0.20 ^d	0.17 ^{c,d}	0.28	0.18 ^d
mSCQ + EAMs + fractures	0.42 ^c	0.34	-0.34 ^d	0.20 ^d	0.17 ^{c,d}	0.27	0.17 ^{c,d}
mSCQ + EAMs + osteoporosis + fractures	0.42 ^c	0.34	-0.34 ^d	0.20 ^d	0.17 ^{c,d}	0.28	0.17 ^{c,d}
RDCI ^b	0.44 ^c	0.25 ^{c,d}	-0.22 ^c	0.12 ^{c,d}	0.08 ^{c,d}	0.17 ^{c,d}	0.10 ^{c,d}
Patients fulfilling ASAS pSpA criteria (n = 415)							
mSCQ	0.40	0.46 ^d	-0.29 ^d	0.19 ^d	0.29 ^d	0.32 ^d	0.25 ^d
mSCQ + EAMs	0.45 ^c	0.35 ^c	-0.29 ^d	0.15 ^{c,d}	0.22 ^{c,d}	0.27 ^c	0.19 ^{c,d}
mSCQ + fractures	0.40	0.41 ^{c,d}	-0.30 ^d	0.18 ^d	0.30 ^d	0.33 ^d	0.26 ^d
mSCQ + osteoporosis + fracture	0.40	0.42 ^d	-0.31	0.19 ^d	0.32 ^{c,d}	0.34 ^d	0.26 ^d
mSCQ + EAMs + osteoporosis	0.45 ^c	0.36 ^c	-0.27 ^d	0.16 ^{c,d}	0.24 ^{c,d}	0.28	0.19 ^c
mSCQ + EAMs + fractures	0.45 ^c	0.37 ^c	-0.26 ^{c,d}	0.15 ^{c,d}	0.24 ^{c,d}	0.27 ^c	0.19 ^{c,d}
mSCQ + EAMs + osteoporosis + fractures	0.46 ^c	0.37 ^c	-0.27 ^d	0.15 ^{c,d}	0.26 ^{c,d}	0.29	0.20 ^{c,d}
RDCI ^b	0.42	0.35 ^{c,d}	-0.23 ^c	0.16 ^{c,d}	0.25 ^{c,d}	0.24 ^{c,d}	0.22 ^{c,d}

^aWork productivity in those currently employed. ^bThe RDCI was calculated according to the information from the physician, except for depression which was retrieved from the patient. ^cDifference of comorbidity score with mSCQ score >10%.

^dDifference on correlation between axSpA and pSpA >10%. EAM: extra-articular manifestations; EQ-5D: Euroqol 5D; mSCQ: modified self-administered comorbidity index; RDCI: rheumatic disease comorbidity index; WPAI: work productivity and activity impairment.

In a previous study, we showed that the mSCQ was a valid comorbidity instrument in 98 patients with longstanding AS, who were included in the OASIS cohort in the Netherlands, Belgium and France [10]. In that study, the mean score of the mSCQ was 2.9, compared with 1.9 in the present study. This may be caused by a higher age of patients in the OASIS cohort (53.9 vs 43.6 years). With respect to construct validity, slightly different instruments were used in the OASIS study compared with the ASAS-ComoSpA study. Correlation of the mSCQ with the BASFI was higher in the OASIS study (0.41) compared with the present study (0.31), whereas correlation between the mSCQ and quality of life was comparable (0.32 with ASQoL and -0.33 with EQ-5D). Differences in correlations may be caused by a more heterogeneous population, a younger age and lower comorbidity scores in the present study.

Although the mSCQ includes many prevalent and important comorbidities, it ignores specific diseases that

occur more frequently in patients with SpA that potentially influence functioning and health, such as EAMs, osteoporosis and fractures. Along these lines, we confirm a high proportion of patients with SpA reporting one or more EAMs (18.8% AAU, 22.1% psoriasis and 7.2% IBD). Obviously, the prevalence of psoriasis was higher in patients with pSpA compared with axSpA. Nevertheless, these results are in line with a previous study that showed high prevalence of EAMs in patients with AS (24.5% of patients have AAU, 10.1% of patients have psoriasis and 7.5% of patients have IBD) after a disease duration of 20 years [22]. Differences in reported EAMs between the different world regions were found and may partly be caused by genetic aspects. Importantly, the agreement between self-reported EAMs and EAMs as confirmed by the study investigator was high for all EAMs. This confirms that patients are highly capable of self-reporting these conditions.

We hypothesized that adding EAMs to the mSCQ would improve construct validity of the questionnaire. However, except for the correlation with age, we could not show this for other external outcomes and some correlations even worsened. Probably, the impact of other comorbidities on health outcomes is more important than the impact of EAMs on these outcomes, which is in line with a previous study that showed that EAMs do not influence long-term health outcomes in patients with AS [23]. This was also reflected by the fact that only a small proportion of patients answered in the mSCQ that the EAM impacted their functioning.

In addition, osteoporosis and fractures are common comorbidities in patients with SpA. Studies have shown that 19–62% of patients with AS have decreased BMD and that the prevalence of spinal fractures ranges between 1% and 9% [24, 25]. Osteoporosis and fractures may be a result of constant low-grade inflammation, disease-specific factors or immobility (such as spinal rigidity). The agreement between self-reported osteoporosis and fractures, and physician-reported osteoporosis and fractures was weak in the present study. This might be a result of different definitions used for osteoporosis and fractures by patients and the study investigators. Patients may not be aware that they suffer from osteoporosis, especially when they do not take anti-osteoporosis drugs, or mix up the name osteoporosis with osteoarthritis leading to discrepancies. Also, anti-osteoporosis drugs may be used as prophylaxis, for example because of concomitant steroid use, and according to the study protocol this was considered as osteoporosis, which may overestimate the prevalence of osteoporosis as defined by the physician. With respect to fractures, only non-traumatic fractures were assessed in the ASAS-COMOSPA study, whereas in the SpA-SCQ patients are asked about fractures in general, because we felt that making a distinction between traumatic and non-traumatic fractures would be too complicated in a self-report questionnaire. Furthermore, patients may not be aware of osteoporotic vertebral fractures (as these may be asymptomatic or symptoms may be interpreted as SpA flare), whereas these were scored by the study investigator. In addition to criterion validity, we also evaluated whether adding osteoporosis and/or fractures would improve the construct validity of the mSCQ, but we could not show this.

This study also compared the construct validity of the mSCQ with another validated comorbidity index, the RDCI. The SpA-SCQ showed stronger correlations with different health outcomes compared with the RDCI. Likely, this is explained by the ‘additional’ question in the SCQ on impact of comorbidities on functioning. Furthermore, in the SCQ, patients have the option to report up to three other non-specified medical problems. Interestingly, the most reported ‘other’ comorbidity was fibromyalgia, which may have significant impact on physical and mental health outcomes. This finding is in line with recent studies that showed that fibromyalgia frequently coexists in patients with axSpA [26, 27]. Last, the SCQ is based on self-report, whereas for the RDCI medical

record data were used. These data may also include comorbidities the patient suffered from in the past, but that do no longer have an impact on health outcomes. Although the RDCI had proven validity, we cannot ignore that correlations of the mSCQ with different health outcomes were consistently stronger, and the mSCQ is therefore preferred when these outcomes are studied.

In an era with increasing multinational research, validity of a questionnaire across countries is of interest. Therefore, the construct and criterion validity of the mSCQ were compared between different regions in the world, which showed significant differences. For example, the correlation between comorbidity scores and several constructs, such as physical function and quality of life, was weaker in Asia and North Africa compared with Europe and North and South America. Importantly, there were already considerable differences in baseline characteristics of physical function and quality of life between the different regions. Most likely, cultural aspects both influence patient-reported outcomes and the way comorbidities influence these outcomes.

Strengths of the present study are the large number of patients and the multi-national character of the study. A limitation of the study is that we cannot exclude that the study investigators used the answers of the patients to fill out the physician case report form. This may have overestimated the agreement between self-reported and physician-reported comorbidities. A second limitation is the slightly different definitions of osteoporosis and fractures in the SpA-SCQ and in the investigator part of the study. Therefore, the weak agreement between both may be an underestimation of the actual criterion validity.

In summary, the mSCQ has been shown to be valid in a large number of patients with SpA from different countries. The agreement between patient-reported and physician-reported EAMs was high, but low for osteoporosis and fractures. The construct validity of the mSCQ did not improve by adding EAMs or osteoporosis and fractures to the questionnaire. Therefore, we do not recommend including these extra questions in the mSCQ in patients with SpA. In future studies in patients with SpA, the mSCQ can be used to assess the impact of comorbidities on health outcomes.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

References

- 1 Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:65–73.

- 2 Rudwaleit M, van der Heijde D, Khan MA, Braun J, Sieper J. How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 2004;63:535–43.
- 3 Rudwaleit M, van der Heijde D, Landewe R *et al.* The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777–83.
- 4 Rudwaleit M, van der Heijde D, Landewe R *et al.* The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70:25–31.
- 5 Fortin M, Bravo G, Hudon C *et al.* Relationship between multimorbidity and health-related quality of life of patients in primary care. *Qual Life Res* 2006;15:83–91.
- 6 Ritchie C. Health care quality and multimorbidity: the jury is still out. *Med Care* 2007;45:477–9.
- 7 van der Zee-Neuen A, Putrik P, Ramiro S *et al.* Impact of chronic diseases and multimorbidity on health and health care costs: the additional role of musculoskeletal disorders. *Arthritis Care Res* 2016;68:1823–31.
- 8 van der Horst-Bruinsma IE, Nurmohamed MT, Landewe RB. Comorbidities in patients with spondyloarthritis. *Rheum Dis Clin North Am* 2012;38:523–38.
- 9 Gabriel SE, Michaud K. Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009;11:229.
- 10 Stolwijk C, van Tubergen A, Ramiro S *et al.* Aspects of validity of the self-administered comorbidity questionnaire in patients with ankylosing spondylitis. *Rheumatology* 2014;53:1054–64.
- 11 Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum* 2003;49:156–63.
- 12 Molto A, Etcheto A, van der Heijde D *et al.* Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. *Ann Rheum Dis* 2016;75:1016–23.
- 13 Lukas C, Landewe R, Sieper J *et al.* Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2008;68:18–24.
- 14 Calin A, Garrett S, Whitelock H *et al.* A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;21:2281–5.
- 15 Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis patient global score (BAS-G). *Br J Rheumatol* 1996;35:66–71.
- 16 EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
- 17 Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353–65.
- 18 England BR, Sayles H, Mikuls TR, Johnson DS, Michaud K. Validation of the rheumatic disease comorbidity index. *Arthritis Care Res* 2015;67:865–72.
- 19 de Vet HT, Mokking LB, Knol DL. Reliability. In: de Vet HT, Mokking LB, Knol DL, eds. *Measurement in medicine a practical guide*. Cambridge: Cambridge University Press, 2011: 115–9.
- 20 de Groot V, Beckerman H, Lankhorsta GJ, Bouter LM. How to measure comorbidity. A critical review of available methods. *J Clin Epidemiol* 2003;56:221–9.
- 21 Bakker P, Molto A, Etcheto A *et al.* The performance of different classification criteria sets for spondyloarthritis in the worldwide ASAS-COMOSPA study. *Arthritis Res Ther* 2017;19:96.
- 22 Stolwijk C, Essers I, van Tubergen A *et al.* The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study. *Ann Rheum Dis* 2015;74:1373–8.
- 23 Essers I, Ramiro S, Stolwijk C *et al.* Do extra-articular manifestations influence outcome in ankylosing spondylitis? 12-year results from OASIS. *Clin Exp Rheumatol* 2016;34:214–21.
- 24 Davey-Ranasinghe N, Deodhar A. Osteoporosis and vertebral fractures in ankylosing spondylitis. *Curr Opin Rheumatol* 2013;25:509–16.
- 25 van der Weijden MA, Claushuis TA, Nazari T *et al.* High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: a systematic review. *Clin Rheumatol* 2012;31:1529–35.
- 26 Baraliakos X, Regel A, Kiltz U *et al.* Patients with fibromyalgia rarely fulfil classification criteria for axial spondyloarthritis. *Rheumatology* 2018;57:1541–7.
- 27 Moltó A, Etcheto A, Gossec L *et al.* Evaluation of the impact of concomitant fibromyalgia on TNF alpha blockers' effectiveness in axial spondyloarthritis: results of a prospective, multicentre study. *Ann Rheum Dis* 2018;77:533–40.